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RESEARCH ARTICLE

Comparative Study of Beclomethasone Dipropionate with Salbutamol and Theophylline in Asthmatic Conditions.

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Conflicts of Interest: Nil

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ABSTRACT

Objectives: The objective of the study is to study the comparative actions of combination beclomethasone dipropionate (BDP) with salbutamol and BDP with theophylline and to evaluate the efficacy of both of these therapeutic regimens in all four types of asthmatic conditions.

Methods: A 24 weeks single-center, open-label, randomized parallel-group intervention study was carried out on the various types of asthmatic patients in the district hospital of Dausa, Rajasthan (North India). Identification of the asthmatic patients was done by examining the cardinal features of asthma as per the guidelines of American Thoracic Society for Asthma. The study was conducted by comparing the efficacy of Theophylline plus BDP 400µg/day against Salbutamol plus BDP 800µg/day on 84 asthmatic patients. The desired outcome was to assess the effects of both of these combination regimens on the cardinal features of asthma.

Results: The treatment with Theophylline plus BDP leads to significant improvement in all types of asthmatic conditions than the treatment group of Salbutamol plus BDP. In addition, prognostic markers also improved in the patients.

Conclusion: The study demonstrated the clinical equivalence of both of the treatment groups in the control of asthma. The prospective intervention study were showed the significant improvement in the treatment group A i.e. Theophylline plus BDP 400µg/day than the treatment group B i.e. Salbutamol plus BDP 800µg/day. The addition of Theophylline with low-dose inhaled corticosteroid therapy is a suitable alternative than latter for patients with all four types of asthma who are not adequately controlled in low-dose inhaled corticosteroids. Therefore, it can be concluded that the former treatment is superior to the latter in improving lung function, decreasing symptoms and need for rescue medication in asthma.

Keywords: **Asthma, BDP, Theophylline, Salbutamol, Corticosteroids.**

Introduction

Asthma is associated with inflammation and suffocation of airway wall so patients feel difficulty in breathing and may start tachypnea. It is a heterogeneous disease defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation [Global Strategy for Asthma Management, 2020]. The definition was based on consideration of the characteristics that are typical of asthma and distinguish it from other respiratory diseases. It is characterized by chronic inflammation of the airways in which there is an overabundance of eosinophils, mast cells, and activated T helper lymphocytes.

These inflammatory cells release mediators that then trigger bronchoconstriction, mucus secretion, and remodeling [Hamid *et al.,* 2009]. Bronchial asthma is a condition in which narrowing of airway due to mucosal edema so patients start to feel dyspnea and sometimes wheezing may occur [Harvey *et al.,* 2009]. The inflammatory mediators that drive this process include cytokines, chemokines, growth factors, lipid mediators, immunoglobulins, and histamine. The inflammation in allergic asthma can be difficult to control. This is mainly due to the development of an adaptive immunity to an allergen, leading to immunological memory [Hamid *et al.,* 2009, Bochner *et al.,*1994]. Mast cells present in wall of alveoli have histamine, LT, and PAF mainly in it. While chemoreceptors present in blood that are O2 and CO2 sensitive means if decrease oxygen concentration in blood it send message to brain and increase breathing and tachypnea occur.

Initially we try to protect rupture of mast cells present in alveoli to avoid drainage of histamine, LT, and PAF. In acute condition inhalation method is more effective than oral syrup and oral tablets [Joel *et al.,* 2001].

A study confirms that 1 out of every 10 asthma patients in the world are from India. According to globalasthmareport.org among India's 1.31 billion people, about 6% of children and 2% of adults have asthma [World Asthma Day, 2021].

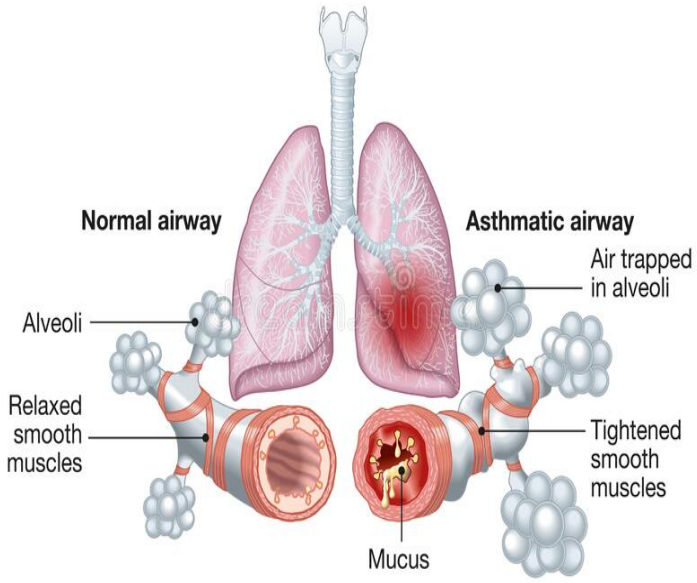


Figure 1: The difference between normal and asthmatic airway

Adapted from Asthma, Normal and Asthmatic Airways, Illustration of aerosol, alveoli: 177704141 Dreamstime.com.

AIM AND OBJECTIVES

AIM

To study the comparative actions of combination beclomethasone dipropionate (BDP) with salbutamol and BDP with theophylline.

OBJECTIVES

- To determine and evaluate the efficacy of both of these combination therapeutic regimen in all four types of asthmatic condition. And To compare these combinations in all those asthma.

RATIONALE OF THE STUDY

To evolve highly effective drugs for the management of asthma that has led to a marked reduction in hospital admissions and mortality for this increasingly common disease. Most patients with asthma are now able to lead a normal life through the use of medications that are virtually free of side effects and to develop any new classes of drug that are more effective than existing agents. The advances in asthma therapy have been largely through improving the selectivity and duration of action of existing

effective classes of drugs. With respect to this, pharmacology has played an important role in validating drug targets and drug design. Pharmacology, particularly through the use of selective agonists and antagonists, has also played an important role in increasing our understanding of the underlying inflammatory mechanisms of asthma, providing a rational basis for the use of current drug therapy. The history of asthma treatment goes back to thousands of years, but most of the important advances have been made during the last 75 years. Autonomic pharmacology, which evolved and has always been very strong in the U.K., has played a particularly important role in the development of bronchodilators and British pharmaceutical companies have played (and continue to play) a leading role in the development of asthma medications, supported by strong interactions with basic and clinical pharmacologists.

MATERIALS AND METHODS

6.1 Study Site:

The study was carried out on the various types of asthmatic patients in the district hospital of Dausa, Rajasthan (North India).

6.2 Study Design:

The study was single-center, open-label, randomized parallel-group intervention study.

6.3 Study Duration:

The total duration of the study was 6 months in the year of 2021-2022.

6.4 Study Sample:

Sample size was calculated using following formula at 95% level of confidence interval and 5% margin of error (ε).

Sample size n' is given by:-

$$n = \frac{z^2 \times \hat{p}(1-\hat{p})}{\varepsilon^2} \rightarrow n' = \frac{n}{1+\frac{z^2 \times \hat{p}(1-\hat{p})}{\varepsilon^2 N}}$$

Where N is the population size, z is the z-score and p^ is the population proportion.

Therefore, N= 140 (Pilot Study); z = 1.96; p^= 50%

$$n = \frac{(1.96)^2 \times 0.5\,(1-0.5)}{(0.05)^2} = 384.16$$

$$n' = (384.16)/\,[1 + (384.16/140)] = 102.60$$

$$\sim 100$$

As per estimated sample size calculation, 100 patients who met the inclusion criteria, enrolled in the study.

6.5 Study Criteria:

Patients were selected based on the following inclusion and exclusion criteria:

❖ **Inclusion Criteria:**

- Both male and female patients aged between 18-70 years.
- Patients having all four types of asthma

I. Mild intermittent asthma
II. Mild persistent asthma
III. Moderate persistent asthma
IV. Severe persistent asthma

- Patients who were willing to participate in the study by signing the informed consent form.

❖ **Exclusion Criteria:**

- Patients who were not willing to give written informed consent.
- Patients who had cold, cough, pneumonia.
- Patients having normal breathing with normal tidal volume and vital capacity.
- Patients having pseudo asthmatic symptoms but did not have asthma.
- Patients who were passed in physical examination of inspiratory and expiratory tests were excluded from the study.

❖ **Withdrawal Criteria:**

- Subjects can withdraw from the study at the discretion of the investigation or sponsor due to a safety concern or if judged non-compliant with study procedures. A subject can be withdrawn from study if one of the following applies:

a. Subject chooses to withdraw from the study at any time.
b. Intolerable adverse effects.
c. Major violation of the study protocol.
d. If any patient may died during treatment.
e. If any subject change the medical practitioner during the study.

The entire study was designed to be conducted in three phases.

6.6 Plan of Work:

PHASE I

- Detailed literature review, done extensively using tertiary resources, secondary resources, primary resources.
- Procure the necessary documentation: Designing of data entry form, informed consent document, patient information sheet.
- Ethical committee approval: Ethical clearance was obtained from the Institutional Ethics Committee.

PHASE II

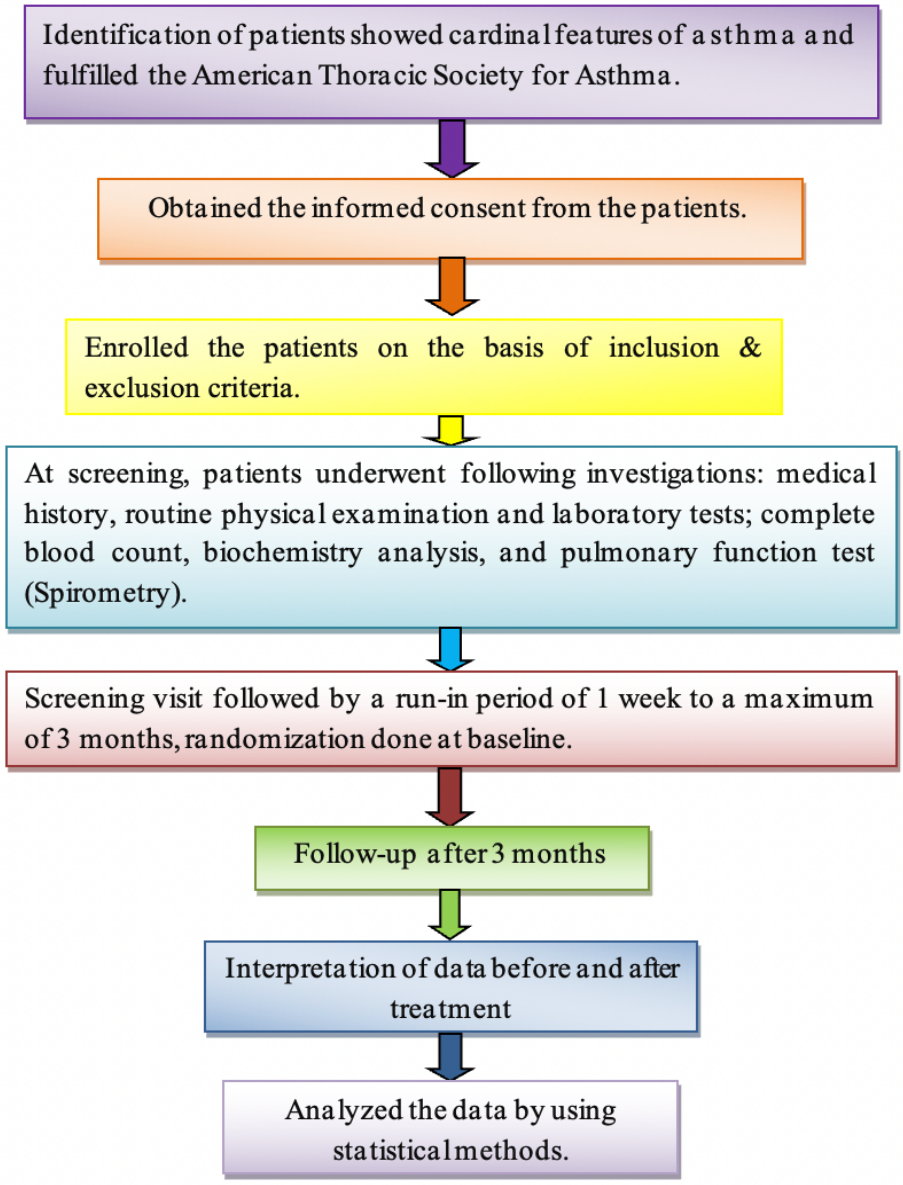
The sample size was collected, which comes under the inclusion and exclusion criteria at the time of enrolment.

- Data were collected using data entry form after explaining the patient information sheet and signing informed consent document.

PHASE III

- Reports were analyzed using various statistical tools.
- Reporting of results and presentation.

6.7 Procedure:



Graph 1:

Observation & Results

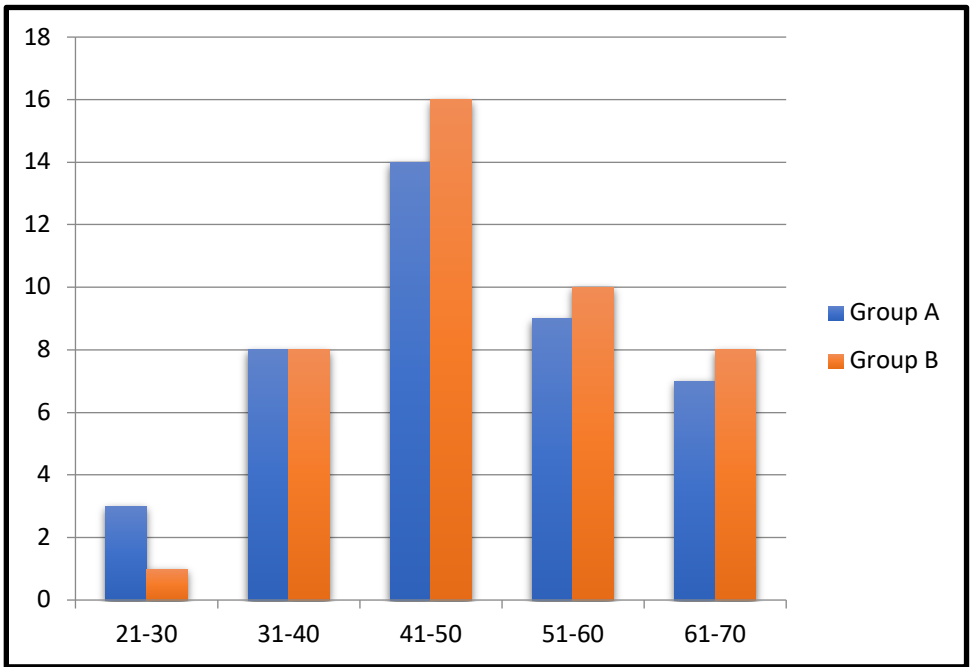
We screened 140 patients of all four types of asthma who presented at the district hospital of Dausa, Rajasthan. After screening for the inclusion and exclusion criteria, out of one forty patients, one hundred patients were randomized for the treatment. Among them, 50 patients were randomly allocated to group A (Theophylline plus BDP 400µg/day) and remaining 50 patients were allocated to group B (BDP with matched placebo [Salbutamol] 800µg/day group). After randomization, 9 patients were withdrawn from group A and 7 patients were withdrawn from group B due to adverse events, violation of inclusion criteria, withdrew consent, non-clinical reason, and discontinued due to inconvenience shown in the Figure no. 11.

At the time of analysis, 41 patients of group A and 43 patients of group B completed the study as per protocol and had valid measurements of the primary variables at baseline and the follow-up after 3 months.

Table 1: Age group wise distribution

Age group (years)	No. of patients in group A (n=41)	% of patients of group A	No. of patients in group B (n=43)	% of patients of group B
21-30	3	7.31	1	2.32
31-40	8	19.51	8	18.60
41-50	14	34.14	16	37.20
51-60	9	21.95	10	23.25
61-70	7	17.07	8	18.60

Out of 84 patients of two groups (Group A & B), total 4 patients were under the age group of 21-30, 16 patients underwent the age group of 31-40, 30 patients were under the age group of 41-50, 19 patients in the age group of 51-60, and 15 patients lied in between 61-70 age group. Patients in the age group of 41-50 were increasing in number of both of these treatment groups.

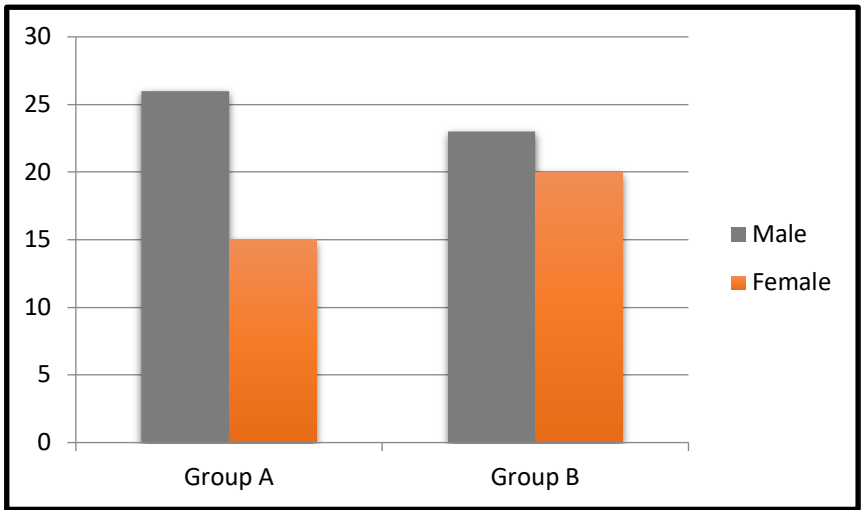


Graph 2: Graphical representation of the age distribution of the treatment groups

Table 2: Gender wise distribution

Gender	No. of patients in group A (n=41)	% of patients of group A	No. of patients in group B (n=43)	% of patients of group B
Male	26	63.4%	23	53.4%
Female	15	36.5%	20	46.5%

From the above table, out of the 84 patients, 49 (58.33%) of both of the treatment groups were males and 35 (41.66%) of patients were females. This observation showed that the male patients allocated in the both treatment groups were mostly affected by asthma than the female patients.



Graph 3: Graphical representation of the gender distribution of the treatment groups

Table 3: Assessment of FEV_1 (L) in treatment group A

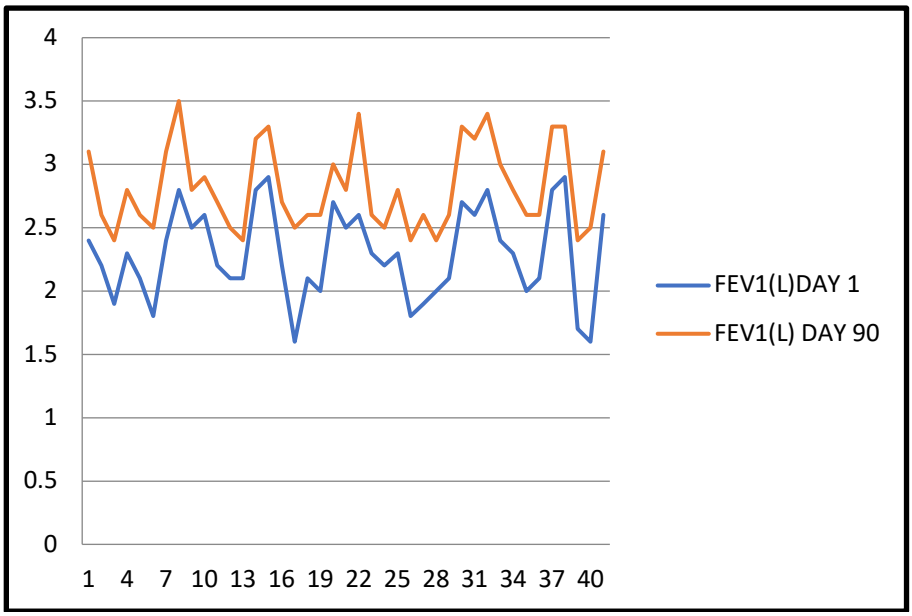
S.NO.	FEV_1(L) Day 1	FEV_1(L) Day 160
1	2.4	3.1
2	2.2	2.6
3	1.9	2.4
4	2.3	2.8
5	2.1	2.6
6	1.8	2.5
7	2.4	3.1
8	2.8	3.5
9	2.5	2.8
10	2.6	2.9
11	2.2	2.7
12	2.1	2.5
13	2.1	2.4
14	2.8	3.2
15	2.9	3.3
16	2.2	2.7
17	1.6	2.5
18	2.1	2.6
19	2.0	2.6
20	2.7	3.0
21	2.5	2.8

22	2.6	3.4
23	2.3	2.6
24	2.2	2.5
25	2.3	2.8
26	1.8	2.4
27	1.9	2.6
28	2.0	2.4
29	2.1	2.6
30	2.7	3.3
31	2.6	3.2
32	2.8	3.4
33	2.4	3.0
34	2.3	2.8
35	2.0	2.6
36	2.1	2.6
37	2.8	3.3
38	2.9	3.3
39	1.7	2.4
40	1.6	2.5
41	2.6	3.1

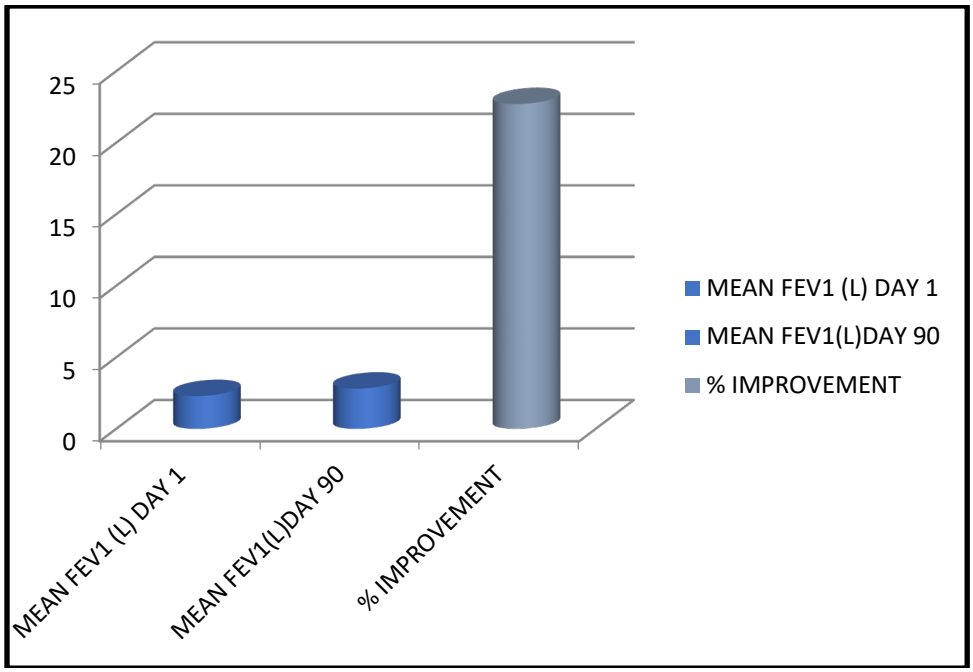
Table 4: Percentage improvement of treatment group A

MEAN FEV_1 (L) DAY 1	MEAN FEV_1 (L) DAY 90	% IMPROVEMENT
2.29	2.81	22.70

The two tailed P value is <0.001, considered as extremely significant.
Mean difference =0.52 (Mean of column B minus Mean of column A).
Out of 84 patients, 41(48.8%) were in treatment with Theophylline plus BDP. Patients showed improvement in asthma with mean value of 22.70%.



Graph 4: Assessment of FEV_1 in treatment group A



Graph 5: Percentage improvement of FEV_1 (L) in treatment group A

Table 5: Assessment of FEV_1 (L) in treatment group B

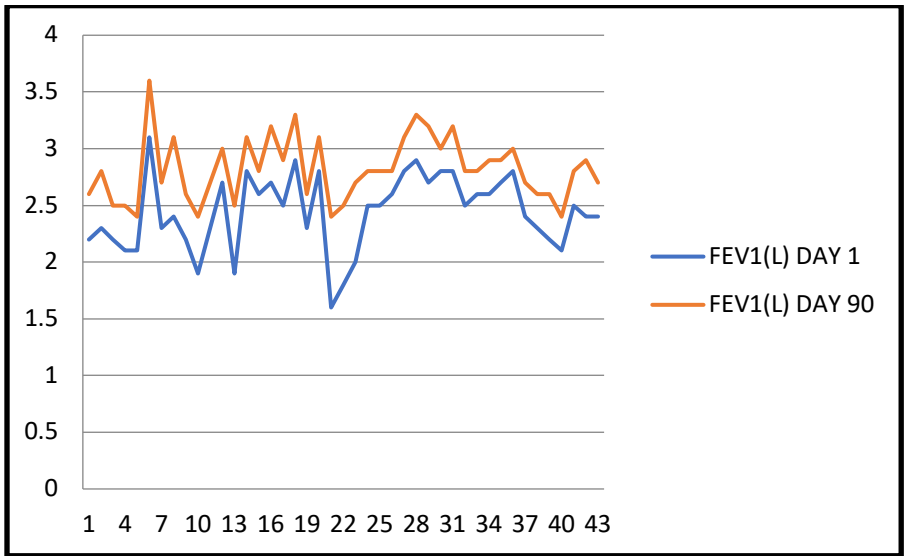
S.NO.	FEV_1(L) Day 1	FEV_1(L) Day 160
1	2.2	2.6
2	2.3	2.8
3	2.2	2.5
4	2.1	2.5
5	2.1	2.4
6	3.1	3.6
7	2.3	2.7
8	2.4	3.1
9	2.2	2.6
10	1.9	2.4
11	2.3	2.7
12	2.7	3.0
13	1.9	2.5
14	2.8	3.1
15	2.6	2.8
16	2.7	3.2
17	2.5	2.9
18	2.9	3.3
19	2.3	2.6
20	2.8	3.1
21	1.6	2.4
22	1.8	2.5
23	2.0	2.7
24	2.5	2.8
25	2.5	2.8
26	2.6	2.8
27	2.8	3.1

28	2.9	3.3
29	2.7	3.2
30	2.8	3.0
31	2.8	3.2
32	2.5	2.8
33	2.6	2.8
34	2.6	2.9
35	2.7	2.9
36	2.8	3.0
37	2.4	2.7
38	2.3	2.6
39	2.2	2.6
40	2.1	2.4
41	2.5	2.8
42	2.4	2.9
43	2.4	2.7

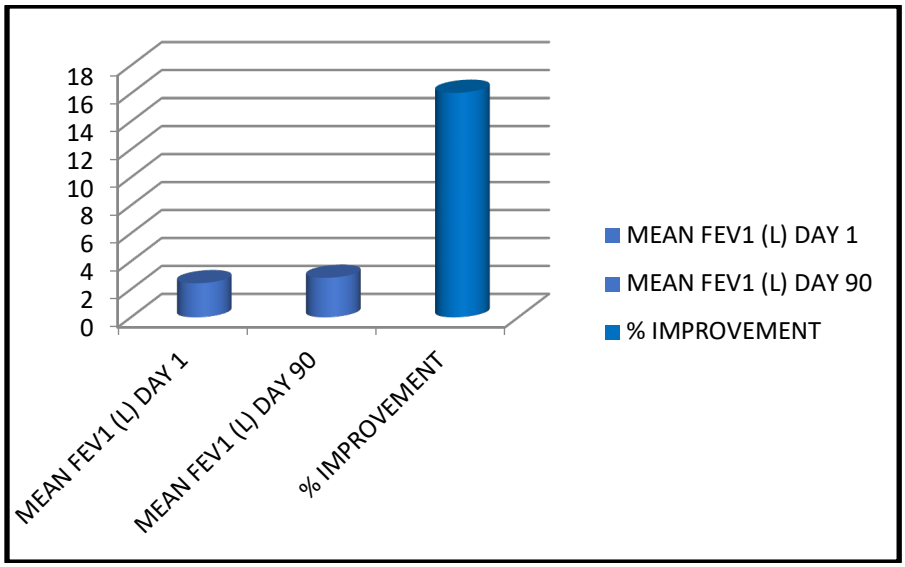
Table 6: Percentage improvement of treatment group B

MEAN FEV_1 (L) DAY 1	MEAN FEV_1 (L) DAY 90	% IMPROVEMENT
2.43	2.82	16.04

The two tailed P value is <0.002, considered as extremely significant.
Mean difference = 0.39 (Mean of column B minus Mean of column A).
Out of 84 patients, 43(51.19%) were in treatment with BDP plus Salbutamol. Patients showed improvement in asthma with mean value of 16.04%.



Graph 6: Assessment of FEV_1 in treatment group B

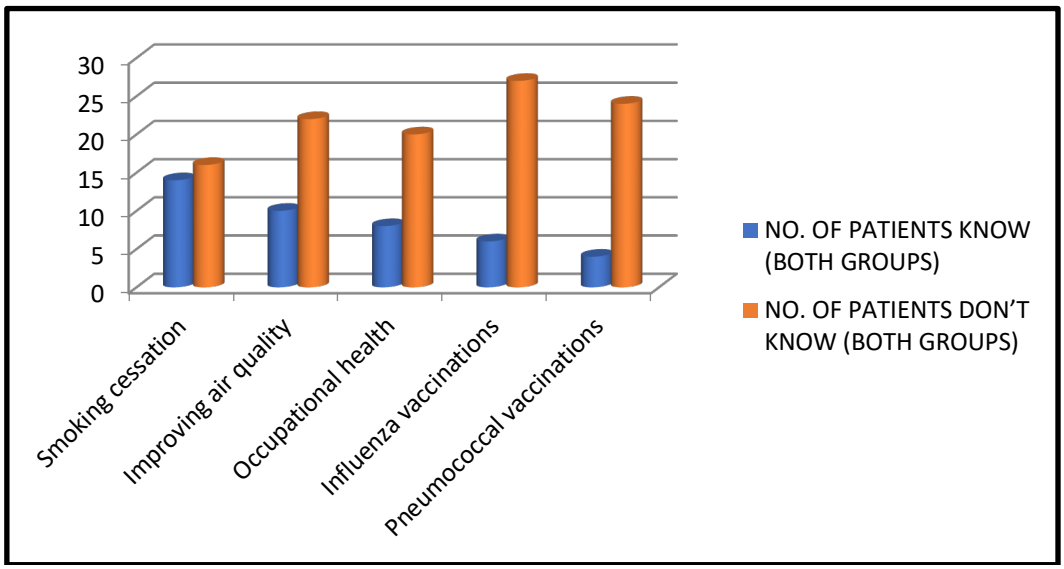


Graph 7: Percentage improvement of FEV_1 (L) in treatment group B

Table 7: Prevention wise distribution of both of the treatment groups

PREVENTION	NO. OF PATIENTS KNOW (BOTH GROUPS)	NO. OF PATIENTS DON'T KNOW (BOTH GROUPS)
Smoking cessation	14	16
Improving air quality	10	22
Occupational health	8	20
Influenza vaccinations	6	27
Pneumococcal vaccinations	4	24

In commonly, most of the patients don't know about the preventive measures for asthma.
15% of people did not quit smoking, 20% of patients did not improve air quality, 18% of patients did not know about their occupational health, 25% of patients did not take influenza vaccinations, and 22% of patients did not receive pneumococcal vaccinations for the prevention of asthma.



Graph 8: Prevention wise distribution

Table 8: The mean peak expiratory flow (PEF) of patients of asthma (Baseline):

PARAMETERS (L/min)	TREATMENT GROUP A	TREATMENT GROUP B
Morning PEF	345±95	344±105
Evening PEF	368±106	368±110
Average PEF	356±99	356±106

The median PEF variability improved significantly in both the treatment groups throughout the study.

Conclusion

Our study demonstrated the clinical equivalence of both of the treatment groups in the control of asthma. The prospective intervention study were showed the significant improvement in the treatment group A i.e. Theophylline plus BDP 400µg/day than the treatment group B i.e. Salbutamol plus BDP 800µg/day. The addition of Theophylline with low-dose inhaled corticosteroid therapy is a suitable alternative than latter for patients with all four types of asthma who are not adequately controlled in low-dose inhaled corticosteroids. Therefore, it can be concluded that the former treatment is superior to the latter in improving lung function, decreasing symptoms and need for rescue medication in asthma.

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